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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,789	11/05/2003	Victor J. Dzau	18989-028	7439

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
03/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,789	DZAU ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/19/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 92-97* is/are pending in the application.

4a) Of the above claim(s) *4-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12 and 92-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/19/07 has been entered.

The amendment and response filed 2/19/2008 are acknowledged. Claims 1, 94 have been amended, claims 13-91 have been canceled, and claims 96, 97 are newly submitted. Claims 4-11 are withdrawn from consideration. Claims 1-3, 12, 92-97 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and new grounds of rejections will not be reiterated. The arguments in 2/19/08 response would be addressed to the extent that they apply to current rejection.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied

with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/423,805 and 60/493,874, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The provisional applications do not disclose SDF-1. Accordingly, the priority date for the claimed subject matter as related to SDF-1 has been established as the filing date of this application, i.e. November 5, 2003.

Alternatively, the applicant is invited to specifically point out where in the priority documents the support could be found.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of Claims 94, 95 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the teaching of *Penn et al* (US 2004/0037811, see discussion under 35 USC §103), i.e. the state of art provides proper enablement disclosure for using SDF-1 and other cytokines for repair of myocardial tissue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 96, 97 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *Greenberger et al* (US 5,993,801), and *Shake et al* (Ann Thorac Surg 2002;73:1919-26), and as evidenced by *Matsui et al* (Circulation 1999;100:2373-9).

Matsui et al teach a method for treating cardiac injury comprising administering an adenoviral vector comprising a nucleic acid encoding a constitutively active Akt via left thoracotomy into the anteroapical myocardium of cardiac ischemia model rats, and reported that Akt activation at the site of cardiac ischemia not only reduced cell death

and size of the infarction, but also dramatically improved regional cardiac functions (e.g. the abstract).

Claim 1 has been amended to recite "wild type" akt gene. *Matsui et al* used a myr-akt "mutant". However, a closer look of the structure of the myr-akt fusion protein (see Matsui 1999, page 2374, column 2), one would find the change was not on wild type akt gene, but addition of epitope tag and membrane targeting signal (myristolation was known in the art to target the expression to membrane and HA-tag was known in the art for easy detection), and hence the wild-type akt was present in the construct disclosed by *Matsui et al* and performed the same function as the wild-type akt.

Matsui et al do not teach administering a mesenchymal stem cell genetically modified to express the akt gene.

Greenberger et al remedy the deficiency by establishing it was well known in the art that bone marrow stromal cells (mesenchymal stem cells) could be used as carriers for delivering an exogenous gene to a patient in need of such transgene (e.g. claims 1 and 2).

Shake et al remedy *Matsui et al* in view of *Greenberger et al* by establishing that it was well known in the art that mesenchymal stem cells are capable of differentiating into cardiomyocytes, and thus could be used for repairing damaged cardiomyocytes. *Shake et al* transplanted MSCs to a swine myocardial infarction model, and reported "robust engraftment", and therapeutic effect, i.e. markedly reducing the extent of wall thinning after the infarction. At the end of the experiment, i.e. *four weeks* after

transplantation, the implanted MSCs could be seen in all treated animals (e.g. the abstract and figure 5).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Matsui et al*, with that of *Greenberger* and *Shake et al*, by administering mesenchymal stem cells expressing an exogenous Akt gene in place of the adenoviral vector with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because not only MSC was a well known transgene carrier but also have the potential to directly repair/regenerating cardiomyocytes. Given that each of the cited references teaches an agent that is effective in cardiac tissue repair/regeneration and in gene transfer, one would have had a reasonable expectation of success combining the akt nucleic acid and mesenchymal stem cells. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant first argue *Matsui et al* results are based on a constitutively active mutant, while claims now require a wild-type akt.

In response, the myr-akt mutant taught by *Matsui et al* modifies the akt by adding a HA epitope tag for easy detection, and a myristoylation signal, which is a post-translation modification so that the akt expression is targeted to membrane. As such, the structure and function of the akt was the same as that of the wild type akt, the akt cDNA itself was not modified.

As to the manner of akt expression, it is noted the claims do not require inducible expression, and encompass constitutive expression. As to an inducible expression, it was well known in the art as taught by *Matsui et al* that akt is *activated* by several cardio-protective ligand-receptor systems, and the expression of akt protected the cell damage induced by hypoxia (e.g. column 1, page 330), and thus *Matsui et al* were well aware of the association between hypoxia and akt. To this end, it is noted the applicant also used constitutive expression in their working examples (e.g. Specification, page 38, 1st zpar).

As to the length of survival for MSCs, *Shake et al* provided evidence that engrafted MSCs could survival at least 4 weeks (end point of experiment).

Arguments about the WO reference were moot since it no longer is the base of the rejection.

Accordingly for reasons set forth *supra*, the rejection stands.

Claims 12 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *Greenberge r et al* (US 5,993,801), and *Shake et al* (Ann Thorac Surg 2002;73:1919-26)as applied to claims 1-3, 96, 97 above, and further in view of *Palasis et al* (US 2002/0172663), for reasons of record and *supra*.

Claims 12, 92-95 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *Greenberger et*

al (US 5,993,801), and *Shake et al* (Ann Thorac Surg 2002;73:1919-26) as applied to claims 1-3, 96, 97 above, and further in view of *Penn et al* (US 2004/0037811).

The combined teaching of *Matsui et al*, in view of *Greenberger et al* and *Shake et al* do not teach using SDF-1 or a growth factor for treating myocardial infarction.

Penn et al supplemented the deficiency by establishing it was known in the art that many cytokines such as G-CSF could increase stem cell homing to injured cardiac tissue, and enhance recovery. *Penn et al* teach a growing body of literature suggests that stem cell mobilization to the heart and differentiation into cardiac myocytes is a naturally occurring process, but insufficient to result in meaningful recovery after myocardial infarction (paragraph 0004). Hence, *Penn et al* teach to enhance the process by directly injecting stem cells, or by administering a nucleic acid encoding stem cell homing cytokines, and by supplying a nucleic acid encoding SDF-1, or cells transfected with the nucleic acids (e.g. paragraph 0005-0009, figure 5). Figure 5 shows the combined effect of SDF-1 and G-CSF was better than any single one alone.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method taught by *Matsui et al* in view of *Greenberger* and *Shake et al*, with that of *Penn et al* by administering mesenchymal stem cells expressing an exogenous Akt gene, a G-CSF gene and/or SDF-1 gene with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to combine the two methods because the combined method may enhance treatment effect. Given that each of the cited references teaches an agent that is effective in cardiac tissue repair/regeneration and in gene transfer, one would have had

a reasonable expectation of success using mesenchymal stem cells for expressing the akt nucleic acid. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30Am to 7pm Monday through Thursday, Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633

QJL
March 26, 2008